Rates of Serious Gastrointestinal Events from Low Dose Use of Acetylsalicylic Acid, Acetaminophen, and Ibuprofen in Patients with Osteoarthritis and Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** The frequency of serious gastrointestinal (GI) complications has been quantitated with chronic high doses of nonsteroidal antiinflammatory drugs (NSAID), but risk at lower dosages remains unknown. We examined the prevalence of serious GI events in patients taking aspirin (ASA), acetaminophen (APAP), or ibuprofen (IBU), focusing on low or intermittent use.

Methods. We studied 5692 patients with rheumatoid arthritis (RA) and 3124 patients with osteoarthritis (OA) from 12 databank centers, with 36,262 patient-years of observation, who had taken one of 3 study analgesics, and examined the frequency of serious GI events requiring hospitalization.

Results. Treatment groups were of similar ages and severity. As lower doses of study analgesics were taken, serious GI events tended to be less prevalent. In patients taking a study drug alone, without other analgesics or corticosteroids, only one event occurred in over 900 patient-years of exposure, roughly equivalent to background. Rates of GI events while taking APAP with other concurrent therapy or corticosteroids were higher ($p < 0.05$) than for the other 2 analgesics. In over-the-counter (OTC) doses, there were no significant differences in GI toxicity among analgesics. RA patients tended to have higher rates than OA patients. The rate of GI events was highly dependent on concurrent therapy, increasing 2 to 6-fold in patients taking other analgesics or corticosteroids. Propensity scores for serious GI events were similar across drugs.

Conclusion. OTC use of ASA, IBU, or APAP carries little risk of serious GI toxicity for most persons. Most serious problems encountered were in higher-risk patients. Given the low rates of events, at low or intermittent dosage without concurrent treatment, these 3 analgesics cannot be distinguished from each other or from background rates of serious GI toxicity. (J Rheumatol 2003;30:2226–33)

Key Indexing Terms:
NONSTEROIDAL ANTIINFLAMMATORY DRUG GASTROPATHY ASPIRIN
IBUPROFEN ACETAMINOPHEN GASTROINTESTINAL TOXICITY

Serious gastrointestinal (GI) events have been well defined in patients who chronically use high doses of nonsteroidal antiinflammatory drugs (NSAID)[1]. They are recognized as the most prevalent serious adverse drug reactions in the United States and have become a major public health concern[2,3]. Different NSAID have different toxicities[4], related in part to their effectiveness at sparing COX-1 inhibition, and to the degree that the effect on platelets is compromised[4,5]. Most studies of NSAID toxicity have been conducted in patients with rheumatoid arthritis (RA) who are taking high doses for prolonged time. These patients may also have comorbid disease conditions and may typically take more than one NSAID or other medications concurrently, such as corticosteroids, which are also associated with increased risk of serious GI complications[1].

Risk for GI events is known to be dose-related for the most part[6], although effects on blood platelets are most pronounced with aspirin (ASA) and occur at low doses on this drug[7]. Acetaminophen (APAP) is not an NSAID, but is often used in similar circumstances and for similar purposes; it has no effects on platelets and inhibits COX-1 and COX-2 to a much smaller extent than NSAID[8]. The comparative toxicity of these analgesic drugs, often taken over-the-counter (OTC), intermittently, and in low doses, has not been well studied, partly because of the lack of datasets that comprise both OTC and prescription drug use.

We examined the prevalence of serious GI events requiring hospitalization in Arthritis, Rheumatism, and

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Aging Medical Information System (ARAMIS) patients with RA and osteoarthritis (OA) taking ASA, APAP, and ibuprofen (IBU) at various dosages, alone and with concurrent therapy, and with a focus on intermittent or less than chronic daily use. We hypothesized that dose-toxicity relationships for intermittent use for the 3 analgesics would converge with each other and with background toxicity rates as doses declined, since even the platelet effects of ASA, which persist for several days after the last dose, would be decreased with intermittent use.

MATERIALS AND METHODS

Patients. We studied 3124 OA patients with 10,120 patient-years of observation and 5692 RA patients with 26,142 patient-years of observation who were drawn from 12 ARAMIS patient groups in the United States and Canada (Stanford, CA; Santa Clara County, CA; Wichita, KS; Saskatoon, SK, Canada; Phoenix, AZ; Cincinnati, OH, Baltimore, MD; Montreal, PQ, Canada; and Pittsburgh, PA). The Stanford, Cincinnati, Montreal, Baltimore, and Pittsburgh patients were drawn from referral institutional practices; Santa Clara County patients are from the community; Saskatoon patients are broadly from patients in the province of Saskatchewan; and Phoenix and Wichita patients are from private rheumatology practices in those cities. The study was approved by the Stanford University Institutional Review Board, and each patient signed an informed consent.

ARAMIS is a prospective observational data bank system in which patients are enrolled consecutively, followed for life, and assessed semiannually for multiple factors, including demographics, socioeconomic status, the biology of disease, the influence of comorbidity, the mechanics and setting of care, specific medical and surgical treatments, and associated costs[9]. The OA patients in this study had confirmed diagnoses of OA, and diagnoses of patients with RA had been documented by their physicians using the American College of Rheumatology criteria for classification of RA, except for the Santa Clara County community sample, in which a random 10% subsample had been physically examined and confirmed to meet these criteria in all instances. Patient characteristics are typical of patients with OA and RA seen in such settings, as described[7].

Measures. Data for this study were collected from patients who had completed the full Stanford Health Assessment Questionnaire (HAQ)[10,11] between 1990 and 1997. The full HAQ is a comprehensive patient outcome assessment instrument that is administered semiannually and collects detailed information on all medications taken over the previous 6 months. Patients report on duration of use, side effects, and side effect severity. They also report on health care resource utilization (hospitalizations, emergency department visits, outpatient surgery, and other medical procedures); comorbid conditions; patient functioning (assessed by the HAQ disability index on a scale of 0–3, where 0 = no disability and 3 = total immobility); pain [assessed by the HAQ pain scale, a double anchored visual analog scale (VAS) from 0–3, where 0 = no pain]; global health status (a VAS from 0–100, where 0 = best possible health); demographic information; and health behaviors. The protocol requires followup of nonresponders, patient contact for missing information, and quality control of questionnaire coding and data entry. ARAMIS procedures result in a 98% to 99% followup per 6-month questionnaire cycle[9]. Reliability and validity of all HAQ variables, including health care resource utilization variables such as number of hospital days and number of physician visits, have been documented[12]. Detailed descriptions of the protocol and methods have been described[9,13,14].

Ascertainment of serious GI events. The primary outcomes for this study were the numbers of serious GI events that required a GI–related hospitalization. Patients with the following kinds of GI events were included in this analysis: NSAID-related upper or lower GI bleeding, clinically symptomatic gastritis, ulcers, gastric outlet obstructions, and GI symptoms serious enough to warrant a hospital admission (abdominal pains or dyspepsia, nausea, vomiting, or diarrhea). GI tract adverse events were determined based on self-report on the HAQ; hospital records for all patients were audited and reviewed to confirm patient report and to insure accurate ascertainment of hospitalizations for GI side effects. All GI events were validated by a physician who was blinded to patient's medication use.

Exposure definitions. We divided drug use into groups according to the medications patients took during the 6-month period covered by the HAQ. Assignment to a drug-use group was based on the patient's most recent self-report and could have been a maximum of 3 months to immediately preceding the time of the GI event. The drug use groups were identified as: "(1) ASA, (2) IBU or (3) APAP Alone," to define periods when patients took only one of the 3 study analgesics and did not take any other NSAID or corticosteroids at the time of that GI event; "(4) ASA, (5) IBU or (6) APAP Plus Concurrent Therapy," to define periods when drug use could have included none, one, or 2 of the other study analgesics or any other NSAID, but not corticosteroids; and "(7) ASA, (8) IBU or (9) APAP Plus Concurrent Therapy & Corticosteroids" to define periods that could have included none, one, or 2 of the study analgesics or any other NSAID, plus corticosteroids. In addition, patients in any of the above groups could have been concurrently taking other medications not known to be associated with serious GI events (e.g., antihypertensive drugs, cardiovascular medications, etc.). Reported dose intervals for the study analgesics were based on commonly available dosage amounts. Results are reported separately for patients with RA and OA.

Statistical analysis. The first incident of a serious GI event was identified for each patient without prior knowledge of the patient's drug exposure. We tallied the frequency of first GI-related hospitalizations by RA and OA patients and by study analgesic (ASA, APAP, IBU). Within each of these 9 groups, first events were tallied by exposure group (ASA, IBU or APAP Alone; ASA, IBU or APAP Plus Concurrent Therapy; or ASA, IBU or APAP Plus Concurrent Therapy & Corticosteroids) and then with dose. Standard errors were constructed for proportions under the assumption that the data constituted a simple random sampling of independent Bernoulli variates from a common population of infinite size[15]. Where reported, nonzero dosages were averaged for that drug up to the time of the patient's first serious GI event. Tests for dose-response patterns were made with logistic regression.

Rates are reported per 1000 patient-years and represent the incidence of first GI events in a drug-use group. Rates were calculated separately for RA and OA patients and by drug-use group and for RA and OA patients and dosage of each drug separately. Rates per 1000 patient-years were calculated as 1000 multiplied by the ratio of Y, the total number of first serious GI events in the dosage group, divided by X, the sum across patient-years until first event or end of observed exposure for that same drug and dosage group (i.e., patients did not contribute additional exposure time after a first event). The nonparametric method given in Cochran[16] for estimating the standard error on a ratio of means was employed, assuming a population of infinite size. Because a separate drug-use group could be created for each dosage group of each drug and usage for each patient, data from the same patient may appear for more than one drug, usage, or dosage group. Because the same patients may appear in more than one dosage group in dose-response relationships, dose-response for rate per 1000 patients was tested via bootstrapping[17]. Specifically, 1250 bootstrap resamples were drawn with the patient (cluster) rather than the encounter serving as the resampling unit. We used 1250 resamples because we found that this provided stability of the tail regions of the distributions. For each resample, Spearman's correlation was calculated between rate and median dosage across the 4 dosage categories; 95% confidence intervals (CI) were then computed from the percentiles of the resampling distribution.

Bootstrap resampling of patients was also used to construct 95% CI on rates per 1000 patient-years (1) for differences among the drug-use group ASA, IBU or APAP Alone; (2) for differences among the drug-use group ASA, IBU or APAP Plus Concurrent Therapy & Corticosteroids; (3) for differences between ASA, IBU or APAP Plus Concurrent Therapy &

Corticosteroids and ASA, IBU or APAP Alone for each drug; and (4) for differences among drugs at lowest dosages. Additionally, bootstrap resampling of patients was used to construct 95% CI on differences in baseline age among the ASA, IBU or APAP Alone group as well as differences in the percentage of patients with at least one serious GI event among the ASA, IBU or APAP Alone group. For all these comparisons CI were constructed from the percentiles of the resampling distribution unless the estimated bias was greater than that accountable for by error due to rounding and resampling rate (e.g., ± 0.1 for rate per 1000 patient-years). Where estimated bias exceeded negligible levels, the "basic" method of Davison and Hinkley[17] was applied unless the raw resampling distribution was clearly skewed, in which case resampling values were logarithmically transformed (with an offset as necessary) and the "basic" method applied with final confidence bounds back-transformed to the original scale. To compare rates per 1000 patient-years between RA and OA patients for the ASA, IBU or APAP Alone group, CI were constructed under the assumption that the sampling distributions of differences in average rates were approximately normally distributed.

Comparison of covariates (sex, baseline age, and baseline pain) between usage categories was multivariate. Centroids on these 3 variables were compared between ASA, IBU or APAP Alone and ASA, IBU or APAP Plus Concurrent Therapy & Corticosteroids categories using a weighted Euclidean distance

$$E = \sqrt{\sum_{i=1}^{3} w_i^2 \, (\bar{y}_{iA} - \bar{y}_{iP})^2},$$

where $\bar{y}_{iA}$ and $\bar{y}_{iP}$ are means for ASA, IBU or APAP Alone and ASA, IBU or APAP Plus Concurrent Therapy & Corticosteroids categories, respectively, of the ith variable. To place each variable on a similar scale, weights employed were 1.0 for sex (w_1), 1/100 for average age (w_2), and 1/3 for average pain (w_3). By this metric, the greatest possible difference in risk was approximately $\sqrt{3} \approx 1.73$. A total of 1250 resamples of patients were employed to construct 95% CI from the percentiles of the resampling distribution on E separately for each drug and disease group.

Additionally, we employed the Stanford Calculator of Risk of Events (SCORE)[18] for each patient in each phase as a propensity score to assess risk of a serious GI event in the next year. The GI SCORE is a reliable and accurate predictor of serious NSAID-related GI events in RA and OA patients[18]. It is based on a multivariable Cox proportional hazards model from study of 566 serious GI hospitalizations in 6386 prospectively followed RA and OA patients with 28,457 patient-years of observation. It simultaneously takes into account 6 predictors [age, type of arthritis (RA/OA), global arthritis health status, proportion of time taking corticosteroids, history of a previous GI side effect, and history of a previous GI hospitalization] that were identified from our previous research and the literature. The GI SCORE is calculated from responses to questions about the 6 predictive factors. For each response a certain number of points are allocated (e.g., age 41–45 years of age = 7 points; 45–50 years of age = 8 points; RA = 2 points, etc.). A score of 10 or less indicates that risk of a serious GI event is relatively low (about 0.2%); 11–15 points indicates that risk is moderately increased to about 1.3%; 16–20 points indicates that risk is increased to about 4.2%; and more than 20 points indicates that risk is increased to more than 8% per year[18]. Since occurrence of a GI event affects the GI SCORE, we stratified each phase of each patient on the GI SCORE from the prior phase. We created 2 strata: (1) GI SCORE of prior phase ≤ 10 to indicate lower risk and (2) GI SCORE of prior phase > 10 to indicate any increased risk, since event numbers were too small for further stratification. Statistics were computed using SAS V.8.2 for Windows.

RESULTS

Patients. Characteristics of the study cohort by disease group are presented in Table 1. Mean years of followup were somewhat higher in RA patients than in OA patients, about 5 and 3 years, respectively. Duration of disease and HAQ pain scores were very similar in both groups. As expected, many RA patients had used corticosteroids at some point, as had some OA patients (most of whom had had only intermittent injection of the knee), but were categorized as steroid users for consistency of interpretation. About 90% of both groups had ever used NSAID at some point. Among patients who reported periods taking only one of the 3 study analgesics (ASA, IBU or APAP Alone group), about one-fifth of RA and one-fourth of OA patients had taken ASA Alone during some period of followup. However, about one-third the rate of RA patients to OA patients (7% vs 19%, respectively) had taken APAP Alone. Twice the rate of OA patients than RA patients had taken IBU Alone (20% and 10%, respectively). When further examined by drug exposure categories, differences in baseline age, sex, and mean duration of disease and other variables were small, and none was statistically significant ($p > 0.05$). In Table 2, which shows the patient numbers and patient years for the 9 drug-use groups, the overall tendency was that higher rates of RA patients than OA patients had used more of the study analgesics and had longer periods of use.

Table 1. Patient characteristics.

	RA Patients	OA Patients
Age, yrs, mean (SE)	57 (0.2)	66 (0.2)
Female, %	75	75
Duration of followup, mean (SE)	4.7 (0.1)	3.0 (0.1)
Disease duration, yrs, mean (SE)	16 (0.2)	17 (0.2)
HAQ pain score: 0 = no pain, 3 = extreme pain, mean (SE)	1.2 (1.0)	1.3 (0.0)
Ever used corticosteroids, %	43.5	10.3
Ever used NSAID, %	90	90
Ever used ASA, APAP, or IBU alone, %		
ASA	20	25
APAP	7	19
IBU	10	20

Serious GI events. Across the 9 drug-use groups, in RA a total of 205 patients had one or more serious GI events; 17 had 2 and one patient had 3 such events. In OA, 65, 7, and one OA patient had one, 2, and 3 serious GI events, respectively. Table 3 shows that the percentage of patients with serious GI events in the study-analgesic Alone and the Plus Concurrent Therapy & Corticosteroids groups was consistently higher in RA patients than in OA patients in each drug-use group, that the occurrence of serious GI events was small, below one percent in the Alone group for each study analgesic, and was consistently lower in OA patients than in RA patients in each of the study analgesic Plus Concurrent Therapy & Corticosteroids groups. ASA percentages in the Alone group were slightly higher, but differences were not statistically significant (95% CI include zero). Note that in

Table 2. Study groups.

	RA Patients, patients/patient-years	OA Patients, patients/patient-years
ASA		
Alone	1117 / 2752	791 / 1396
Plus Concurrent Therapy	1859 / 5155	1534 / 3102
Plus Concurrent Therapy & Corticosteroids	2569 / 7668	1565 / 3177
APAP		
Alone	402 / 390	592 / 489
Plus Concurrent Therapy	1669 / 2836	1821 / 3075
Plus Concurrent Therapy & Corticosteroids	2701 / 5192	1870 / 3215
IBU		
Alone	577 / 974	630 / 823
Plus Concurrent Therapy	1079 / 1859	1263 / 1975
Plus Concurrent Therapy & Corticosteroids	1563 / 2799	1300 / 2056

Table 3. Percentage of patients with a first serious GI event in the "Alone" and "Plus Concurrent Therapy & Corticosteroids" drug-use groups*.

	RA Patients			OA Patients		
	GI Events, n	Patients, n	% (SE)	GI Events, n	Patients, n	% (SE)
ASA						
Alone	11	1117	0.9 (0.3)	4	791	0.5 (0.3)
Plus Concurrent Therapy & Corticosteroids	67	2569	2.6 (0.3)	15	1565	0.9 (0.3)
APAP						
Alone	1	402	0.3 (0.2)	1	592	0.2 (0.2)
Plus Concurrent Therapy & Corticosteroids	78	2701	2.9 (0.3)	37	1870	2.0 (0.3)
IBU						
Alone	3	577	0.5 (0.3)	2	630	0.3 (0.2)
Plus Concurrent Therapy & Corticosteroids	17	1563	1.1 (0.2)	11	1300	0.8 (0.3)

* Because of small patient numbers, drug use categories were collapsed.

Table 3, the sum of events may be less than the total number of events, since events may have occurred when a patient was not using a study analgesic, but could have been taking a non-study drug.

In Table 4 we examine the rates of serious GI events per 1000 patient-years (SE) for the 9 drug-use groups. Rates are lower in OA patients than in RA patients for all groups and had a marked association with concurrent therapy, decreasing by approximately one-half to one-sixth when the Concurrent Therapy group is compared with the study-analgesic Alone group. In RA patients there is a further marked effect of concurrent corticosteroid therapy that is not observed in OA patients, where such concurrent treatment is less common. The values for the study-drug Alone groups

Table 4. Rates of serious GI events per 1000 patient-years by drug-use group.

	RA Patients		OA Patients	
	Patient-Years	Rate (SE)	Patient-Years	Rate (SE)
ASA				
Alone	2752	4.0 (1.2)	1396	2.9 (1.4)
Plus Concurrent Therapy	5155	5.2 (1.0)	3102	4.5 (1.2)
Plus Concurrent Therapy & Corticosteroids	7668	8.7 (1.1)	3177	4.7 (1.2)
APAP				
Alone	390	2.6 (2.6)	489	2.1 (2.1)
Plus Concurrent Therapy	2836	8.8 (1.8)	3075	11.1 (1.9)
Plus Concurrent Therapy & Corticosteroids	5192	15.0 (1.7)†	3215	12.0 (1.9)†
IBU				
Alone	974	3.1 (1.8)	823	2.4 (1.7)
Plus Concurrent Therapy	1859	4.3 (1.5)	1975	5.1 (1.6)
Plus Concurrent Therapy & Corticosteroids	2799	6.1 (1.5)	2056	5.4 (1.6)

† Significantly different ($p < 0.05$) from rates for the other 2 study analgesics in the same drug-use group.

vary from 2.6 to 4.0 and do not differ significantly from each other ($p > 0.05$). They do rise to the literature level (i.e., 12.0 per 1000 patient-years for the average NSAID and about 2.0 per 1000 patient-years for placebo or non-drug controls[19]) when concurrent therapy is allowed for APAP patients. In both RA and OA patients, the rates of GI events for patients in the APAP Plus Concurrent Therapy & Corticosteroids group were statistically higher ($p < 0.05$) than rates for the other 2 study analgesics in the same drug-use group, although the rates in the Alone group were statistically indistinguishable across analgesics.

Dose-response relationships. Dose-response rates of serious events per 1000 patient-years for the Alone and Plus Concurrent Therapy & Corticosteroids groups for the 3 study analgesics are presented in Table 5, and are divided into dose quarters of ≤ 162, 163–1300, 1301–2600, and > 2600 mg for ASA and APAP and ≤ 100, 101–1100, 1101–2200, and > 2200 mg for IBU, with frequency not taken into account and with lowest dosages likely indicating intermittent use. For analysis, data were stratified by dosage level for each drug for each patient. Because in the Plus Concurrent Therapy & Corticosteroids group patients may have been taking more than one study analgesic, other NSAID, or corticosteroids, data from the same patient may appear in more than one dosage stratum in a given dose-response relationship and in more than one dose-response curve across the different drugs.

In RA patients, statistically significant ($p < 0.05$) dose-response effects were seen within APAP and IBU in the Plus Concurrent Therapy & Corticosteroids group, although the number of events was small and the standard error in APAP large. The difference in rates in the study analgesic Plus Concurrent Therapy & Corticosteroids group is statistically indistinguishable between ASA and APAP for both RA and OA patients (95% CI –2.3, 26.6 and 95% CI –12.3, 0.1, respectively), as is the difference between ASA and IBU for OA patients (95% CI –1.0, 7.0). Further, in RA patients the large standard errors for ASA in the lowest dosage stratum (≤ 162 mg) and for the highest dosage stratum (> 2600 mg) in APAP reflect the small numbers of events that occurred. In contrast, the rate at the lowest dosage was greater for APAP than for IBU for OA patients (95% CI 3.1, 14.7), although with large standard errors. Comparisons involving IBU for RA patients were not instructive, as total exposure was too small to detect any events (including background) in these patients. Overall, when examining dosage effects, numbers were small and dose-response patterns inconsistent.

In the study-analgesic Alone group, at the lowest doses there was one event in any of the 3 analgesics across both RA and OA patients. Numbers were too small to reliably estimate dose-response relationships, but comparison with study analgesic use in the Plus Concurrent Therapy & Corticosteroids group shows that the low dose-effects seen with ASA in RA are confined to these patients.

Frequency of use. Table 6 shows the results of examining usage frequency by days per month for each study analgesic, from 1 to 10 days (1 < 10) and 11 to 25 days per month, with 1 < 10 days suggesting intermittent usage. Similarly for both diseases, the number of events was generally small and differences between study analgesics inconsistent.

Risk of having a serious GI event (GI SCORE). Across both RA and OA patients, the great majority of serious GI events

Table 5. Dose-response curves for GI events per 1000 patient-years for the "Alone" and "Plus Concurrent Therapy & Corticosteroids" drug-use groups*.

RA Patients													
	ASA				APAP				IBU				
	Alone		Plus Concurrent Therapy & Corticosteroids		Alone		Plus Concurrent Therapy & Corticosteroids			Alone		Plus Concurrent Therapy & Corticosteroids	
Dose Intervals, mg	Patient-Years	Rate (SE)	Patient-Years	Rate (SE)	Patient-Years	Rate (SE)	Patient-Years	Rate (SE)	Dose Intervals, mg	Patient-Years	Rate (SE)	Patient-Years	Rate (SE)
≤ 162	101	0	419	16.71 (6.3)	127	0	1777	9.57 (2.3)	≤ 100	97	0	339	0
163–1300	987	4.05 (2.0)	2895	9.67 (1.8)	152	6.58 (6.58)	1929	14.00 (2.7)	101–1100	261	0	732	5.47 (2.7)
1301–2600	801	4.99 (2.5)	2207	6.80 (1.8)	72	0	999	25.04 (5.1)	1101–2200	354	2.83 (2.8)	966	5.18 (2.3)
> 2600	873	4.58 (2.3)	2199	8.18 (2.0)	40	0	561	23.19 (6.5)†	> 2200	263	7.60 (5.4)†	771	10.38 (3.6)†
OA Patients													
≤ 162	254	3.94 (3.9)	689	4.37 (2.5)	176	0	1264	10.29 (2.9)	≤ 100	172	0	505	1.98 (2.0)
163–1300	825	2.43 (1.7)	1929	4.67 (1.6)	127	0	950	12.64 (3.7)	101–1100	313	3.19 (3.2)	776	7.74 (3.1)
1301–2600	218	4.59 (4.6)	380	2.64 (2.6)	112	8.97 (9.0)	650	16.92 (5.1)	1101–2200	231	0	548	3.65 (2.6)
> 2600	103	0	189	10.58 (7.5)	74	0	390	10.26 (5.1)	> 2200	110	9.09 (9.0)	232	8.64 (6.1)

† Significantly different between lowest and highest dose range ($p < 0.05$). * Because of small patient numbers, drug-use categories were collapsed.

Table 6. Rates of serious GI events per 1,000 patient-years by frequency of use in the "Plus Concurrent Therapy & Corticosteroids" drug-use group.

	RA Patients					
	ASA		APAP		IBU	
Days/Mo	Patient-Years	Rate (SE)	Patient-Years	Rate (SE)	Patient-Years	Rate (SE)
1–10	514	3.89 (2.7)	1331	5.26 (2.0)	407	2.46 (2.5)
11–25	105	19.05 (13.6)	167	0	96	10.47 (10.2)
	OA Patients					
1–10	593	3.38 (2.4)	906	4.42 (2.2)	493	2.03 (2.0)
11–25	112	8.97 (9.0)	227	0	106	0

Table 7. Risk of serious GI event relative to GI risk SCORE.

	RA Patients							
			Low Risk, GI Score ≤ 10			Increased Risk, GI Score > 10		
	Mean Risk Score	Low Risk, %	Patient-Yrs	N	Rate (SE)	Patient-Yrs	N	Rate (SE)
ASA								
Alone	12.4	28.1	695	1	1.44 (1.4)	1779	9	5.06 (1.7)
Plus Concurrent Therapy	12.5	26.6	1218	2	1.64 (1.2)	3329	22	6.61 (1.4)
Plus Concurrent Therapy & Corticosteroids	13.6	19.9	1333	2	1.50 (1.1)	5354	59	11.02 (1.4)
APAP								
Alone	12.8	24.1	86	0	0	271	1	3.69 (3.7)
Plus Concurrent Therapy	12.8	23.3	615	2	3.25 (2.3)	1960	23	11.74 (2.5)
Plus Concurrent Therapy & Corticosteroids	14.2	15.4	711	3	4.22 (2.5)	3910	75	19.18 (2.2)
IBU								
Alone	11.1	32.8	283	0	0	581	3	5.17 (2.7)
Plus Concurrent Therapy	12.0	31.7	509	0	0	1095	8	7.31 (2.6)
Plus Concurrent Therapy & Corticosteroids	13.0	24.2	579	0	0	1812	15	8.28 (2.1)
	OA Patients							
ASA								
Alone	11.9	25.5	283	1	3.53 (3.5)	827	3	3.63 (2.1)
Plus Concurrent Therapy	12.0	23.3	545	1	1.84 (1.8)	1792	13	7.26 (2.0)
Plus Concurrent Therapy & Corticosteroids	12.1	23.0	550	1	1.82 (1.8)	1838	14	7.62 (2.0)
APAP								
Alone	12.0	25.8	89	0	0	256	2	7.81 (5.5)
Plus Concurrent Therapy	11.9	23.4	534	1	1.87 (1.9)	1748	27	15.45 (2.9)
Plus Concurrent Therapy & Corticosteroids	12.0	23.3	547	1	1.83 (1.8)	1804	25	13.68 (2.8)
IBU								
Alone	11.4	37.7	234	1	4.28 (4.2)	386	0	0
Plus Concurrent Therapy	11.5	32.8	466	2	4.30 (3.0)	953	7	7.35 (2.8)
Plus Concurrent Therapy & Corticosteroids	11.6	32.1	472	2	4.24 (3.0)	1000	8	8.0 (2.8)

SCORE: Stanford Calculator of Risk of Events.

are predicted in the Increased Risk groups (GI SCORE > 10), particularly in RA patients (Table 7). The rates of GI hospitalizations and propensity scores are consistently higher in RA than in OA patients. They tend to increase with concurrent therapy in part because corticosteroid use is included in the propensity score. Average propensity scores across drugs did not differ. The percentage of low-risk patients, however, was greater with IBU than with the other

2 analgesics. The numbers of events in the low-risk groups (GI SCORE ≤ 10) in both RA and OA patients with or without concurrent therapy were very small.

As an estimate of the distribution of high-risk patients across drugs, we calculated the prevalence of low-risk patients for each stratum. Results consistently show that the lowest percentage of low-risk patients are taking the study analgesic with concurrent therapy.

DISCUSSION

NSAID-related gastropathy is recognized as a problem of epidemic proportions, and toxicity at high doses during chronic use has been well characterized and documented[19]. However, intermittent or occasional use, as is standard in the OTC setting, has not been well studied. In this prospective observational study with large numbers of patients with RA and OA, our results show that much of the associated toxicity of ASA, IBU, or APAP is related to use of the analgesic with other concurrent drug use, and when concurrent drug use is excluded, rates of serious GI events among the 3 analgesics are low and statistically indistinguishable, particularly in low-risk patients. Associated concurrent drug therapy could have had a direct effect when the GI event was caused by the joint use of corticosteroids or other drugs. Many studies have confirmed the independent association of corticosteroids with GI events[1], and our data presented here show that rates consistently decreased when corticosteroids and other concurrent therapy were excluded. Alternatively, the use of concurrent therapy by these patients could also have served indirectly as a marker for other comorbidities not examined.

We did not expect to find some of the highest rates of serious GI events in patients taking APAP, since APAP has been generally considered the safest of all OTC analgesics, and there is little plausible biological validity for its association with serious GI events. When analyzed in the study-analgesic Alone group, safety was similar to the other study drugs and to background. However, when taken concurrently with corticosteroids or other NSAID, risks for APAP were the highest for all of the 3 study drugs in both RA and OA, although the numbers of events were relatively small. This suggests that concurrent drug use in those taking APAP was exerting a particularly large effect. Alternatively, APAP could be preferentially given to higher-risk patients, although the similarities in propensity scores suggest that this did not occur. Moreover, the strong dose-response relationship argues against confounding by indication. Recent studies by other groups have also reported similar results[20,21]. We found no evidence for a treatment-indication bias.

We also found that occasional or intermittent use of the study analgesics was associated with low rates of serious GI events, and as hypothesized, that data for the 3 analgesics converged with each other and with background rates. In addition, there were no significant differences in age, sex, or pain levels for each of the study analgesics in the Alone or Plus Concurrent Therapy & Corticosteroids group, whereas these variables have been associated with risk in other studies[19], again suggesting that the APAP Plus Concurrent Therapy groups were not formed of sicker patients. Using the GI score as a validated propensity score, the propensity for serious GI events was similar across drugs.

Because GI events in OTC use were relatively rare and some patient samples only moderate in size, we were unable to separate the "dose-effect" from the effect of "concurrent therapy," except with low statistical power. However, these results show extremely low or even no GI event rates at the lowest dosages in these cohorts of patients with RA and OA. Only one event occurred across both RA and OA patients in over 900 patient-years in the low-dose exposure group in the study-analgesics Alone groups (likely representative of occasional or OTC use). If the effects of dose and concurrent drug use are independent of each other, an inference may be drawn that occasional use in the absence of corticosteroids or NSAID concurrent therapy results in incidence rates similar to background for all 3 analgesics. All drugs, taken alone and in low-risk patients, show an excellent safety profile.

The strengths of this study are the large number of person-years at risk, the ability to adjust for other medications and for propensity scores, the longitudinal makeup of the cohort, and the availability of data on OTC use as well as prescription use. Outcome data had been collected prospectively, and the reliability of ARAMIS patient self-report data has been well documented[12]. Case ascertainment was done without a priori knowledge of medication use. The limitations of these findings include the restriction of the data to patients with RA and OA, and whether or not these results could be generalized to other populations or to patients who are dissimilar demographically from this cohort.

We believe that the findings of our prospective, multiple population-based study reflect the usage of these analgesics by patients with RA and OA. Our study thus lends support to the relative safety of ASA, IBU, and APAP when used in doses and frequencies similar to the most prevalent use of these drugs, particularly in individuals without other concurrent drug therapy.

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